## REMARKS

The Office has maintained the rejection of the claimed invention over the disclosure of WO 99/01450 (which corresponds to US 6,506,767, "the '767 patent") because it is believed that "[c]hanging solvents for recrystallization is routine to those skill [sic] in the art" (see November 3, 2006 Office Action at page 2, line 6).[1] In support of this position, the Office has relied on the expert testimony of Prof. Corey, which was also relied on by the *Eli Lilly Court*, as evidenced by the following passage, with emphasis supplied:

> The record evidence illustrates that while Lilly scientists knew that some solvents for recrystallizing ***fluoxetine hydrochloride*** were more effective than others, choosing a suitable recrystallization solvent was well known to one of ordinary skill in the art. In particular, Dr. Elias J. Corey ("Corey"), a Nobel laureate, testified that ***fluoxetine hydrochloride*** is "generally quite easy to purify by recrystallizaton." Corey also explained that, although it requires some experimentation, selecting a recrystallization solvent is "very straightforward." Further, Barr's expert testified that "in 1974, sometimes the recrystallization of amine hydrochlorides was indeed routine."

*Eli Lilly & Co. v. Barr Labs.*, 251 F.3d 955, 962 (Fed. Cir. 2001).

Applicants believe that the Office's reliance on Prof. Corey's testimony for purposes of generalization is without merit. In all due respect, this testimonial evidence is not relevant to the present matter because the present matter does not involve purification of fluoxetine hydrochloride. Instead the present matter involves ***preparation*** of certain crystalline forms of desloratadine. Applicants believe that the generalization made by the Office is improper because Prof. Corey's testimonial evidence relates to purification of fluoxetine hydrochloride by crystallization, which is an issue that is separate and distinct from preparation of a certain crystalline form of desloratadine. Moreover, Applicants further believe that the Office's

[1] Because the '767 patent corresponds to the '450 publication, Applicants have treated the two disclosures equivalently and cite only to the '767 patent.

generalization is improper because it is contradictory to the express teachings of the '767 patent, which show that solvent selection is not routine because the resultant ratios of certain crystalline polymorphic forms of desloratadine obtained by even similar solvents is not entirely predictable.

Applicants invite the Examiner to consider the following tabulated information that has been culled from the disclosure of the '767 patent. Table 1 shows the crystallization solvents used to prepare certain polymorphic forms of desloratadine, while Table 2 shows the exemplified crystallization solvents used to prepare certain polymorphic forms of desloratadine.

**Table 1.**

| Crystallization Solvent | Citation (Col.: line(s)) | Comments |
|---|---|---|
| hexanol | 4:22 | 100% polymorph Form I |
| methanol | 4:23 | 100% polymorph Form I |
| 3-methyl-1-butanol | 4:24 | significant amounts of Form II |
| cyclohexanol | 4:24 | significant amounts of Form II |
| dichloromethane | 4:25-26 | Form I substantially free of Form II |
| dioxane | 4:28 | Form I substantially free of Form II |
| di-isopropyl ether | 4:29 | Form I with significant amounts of Form II |
| di-n-butyl ether | 4:30 | Favored formation of Form II |
| **methyl isobutyl ketone** | **4:31-32** | **Form I essentially free of Form II** |
| **methyl butyl ketone** | **4:33** | **8:1 ratio of Form I to Form II** |
| ethyl acetate | 4:37 | Form II substantially free of Form I |
| di-n-butyl ether | 4:39 | Form II substantially free of Form I |

**Table 2.**

| Example | Citation (Col.: line(s)) | Crystallization Solvent | Washing Solvent | Comment |
|---|---|---|---|---|
| 1 | 9:63~10:21 | methyl isobutyl ketone (MIBK) | MIBK | % Form I not specified |
| 2 | 10:24-60 | MIBK | MIBK | 1st crystallization: crude material (% of I-to-II unknown). 2d crystallization: 100% of Form I |
| 3-A | 10:63~11:9 | methanol | hexane | % Form I not specified |
| 3-B | 11:10-26 | MIBK | MIBK | 100% of Form I |
| 4 | 11:28-46 | ethyl acetate | hexane | **100%** of Form II |
| 5 | 11:48~12:8 | di-n-butyl ether | n/a | Crystalline solid contained 92% (± 5%) of Form II |

In particular, the Examiner is asked to compare the two solvents: methyl isobutyl ketone and methyl butyl ketone. Although these solvents are similar to one another, the resultant crystalline polymorphic ratio of desloratadine is not similar. For instance, when desloratadine is crystallized from methyl isobutyl ketone the crystalline desloratadine contains polymorphic form 1 essentially free of polymorphic form 2 (see the '767 patent at column 4, lines 31-32).[2] This should be contrasted to the crystallization process of methyl butyl ketone wherein the ratio of polymorphic form 1 to polymorphic form 2 is 8:1 (see the '767 patent at column 4, line 33). Based on the mandate of the '767 patent (see footnote 3 below), crystalline desloratadine obtained by using methyl isobutyl ketone as a crystallization solvent is acceptable for pharmaceutical purposes, but crystalline desloratadine obtained by using methyl butyl ketone as a crystallization solvent is not.[3] Thus, while the Office may consider that it is routine to go to the solvent cabinet and select a certain solvent for crystallization may be routine, the obtained results are far from routine; meaning that the results are unpredictable. Given the fact that the results

[2] The '767 patent at column 3, lines 53-58 specifies that "the phrase 'polymorph form 1 essentially free of polymorph form 2' as used herein means that [desloratadine] polymorph form 1 prepared in accordance with this invention contains less than about 1% of form 2 as measured by infrared spectral analysis on a FTIR spectrometer."

[3] The intent of the '767 patent is to obtain crystalline desloratadine in its two separate forms that are as pure as possible. This can be understood by inspecting the disclosure of the '767 patent at col. 1, lines 34-41, which reads as follows with emphasis added:

> To prepare pharmaceutical compositions containing [desloratadine] for administration to mammals in accordance with exacting health registration requirements of the U.S. and international health registration authorities, e.g. the FDA's Good Manufacturing Practices("GMP")requirements, there is a need to produce [desloratadine] in as pure a form as possible, especially a form having constant physical properties.

The '767 patent further discloses at column 4, lines 5-11 that:

> We have discovered that [desloratadine] exists as a mixture of polymorphs. Such a mixture could lead to production of a [desloratadine] product which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.

Based on the forgoing, one can infer that the intent of the '767 patent is to provide two distinct crystalline forms of desloratadine in which each form is produced "in as pure as form as possible, especially a form having constant physical properties" (see the '767 patent at col. 1, lines 40-41). One can also infer that it is unacceptable to have crystalline desloratadine that is not in as pure a form as possible, because the crystalline material would not have constant physical properties, which is "unacceptable in view of stringent GMP requirements" (see the '767 patent at col. 4, lines 9-11).

are unpredictable, then to maintain an obviousness rejection in view of this information is clearly improper.

Accordingly, the rejection of claims 1-72 under 35 U.S.C. § 103(a) over the disclosure of WO 99/01450 (or in the alternative over US 6,506,767, "the '767 patent") is respectively traversed. Based on the foregoing reasoning and the reasoning set forth in the response filed August 9, 2006, Applicants kindly request that the Examiner withdraw the rejection.

Applicants also ask that the Examiner consider the following reasoning in light of certain passages of the '767 patent that are reproduced below:

> Descarboxyloratine prepared as described in U.S. Pat. No. 4,659,716 was isolated as the acetic acid salt (Example III) and as a mixture of polymorphs of the free base from hexane (see Examples V+VI).

See the '767 patent at column 4, lines 1-4.

From this passage, it is clear that polymorphic forms 1 and 2 were known even before the '767 patent (and the '450 publication), and still the application of the '767 patent was issued. A reason why it was accepted is justified in the next citation from the '767 patent at column 4, lines 5-11:

> We have discovered that descarbonylethoxyloratadine exists as a mixture of polymorphs. Such a mixture could lead to production of a descarbonylethoxyloratadine product which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.

So the innovative part of the '767 patent is that instead of obtaining **variable** mixtures of polymorphs, which according to the '767 patent (see footnote 3 above) are not acceptable by the GMP requirements, it is possible to devise such crystallization systems which permit the preparation of pure polymorphs. In this respect, Applicants note that another alternative to avoid the unacceptable properties of desloratadine prepared by the teachings of the '716 patent is,

however, to prepare mixtures of polymorphs which are **not variable** and therefore are not contradicting the GMP requirements. This is the object of the present application. So what is new is not the forms 1 and 2, which were known even before the filing of the '767 patent, but the fact that they are obtained by reproducible methods which allow to prepare constant (not variable) mixtures of polymorphs. From this point of view it follows that if the claims of the '767 patent are novel and unobvious over the prior art, then so too are the claims of the present application. The innovative aspect of the '767 patent is illustrated in summary by the following citation:

> We have discovered specific solvents and experimental conditions which consistently produce two distinctly different crystalline polymorphs of descarbonylethoxyloratadine thereby allowing commercial production of a consistent pharmaceutical product having constant physical properties.

See the '767 patent at column 4, lines 12-16.

All patents regarding the discovery of crystalline forms are about different solvents and crystallization conditions. If for one skilled in the art this is routine experimentation then no patents regarding crystalline forms should be issued. In particular, this is true for the '767 patent presently used in support of the outstanding rejection. What Applicants intend to protect by way of a patent relates to novel and unobvious solvent systems and conditions. The fact that this patent was accepted means that one skilled in the art cannot foresee just by using arbitrary solvents and crystallization conditions what will be the experimental results and that therefore the suggested solvents and conditions are both novel and unobvious. The same is true for the present application. In order to prepare desloratadine with a constant (and not variable) composition of polymorphs specific conditions were discovered which are different from the conditions mentioned in the '767 and '716 patents. Therefore, if the '767 patent was acceptable to the Office, then so too should the present application.

Applicants request that the Examiner acknowledge the same and withdraw this rejection and pass the present application to issue.

Applicants concurrently filed with the present response a Request for a Three-Month Extension of Time under 37 CFR 1.136(a) with an authorization to charge the requisite fee under 37 CFR 1.17(a)(3) to Applicants' representative Deposit Account 13-2725. If for any reason the Request is separated from the present response, then Applicants authorize the Office to charge the above-noted Deposit Account to pay any necessary fees so as to maintain the pendency of the present application.

In view of the remarks contained herein, Applicants respectfully request a Notice of Allowance. If the Examiner believes that a discussion would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

**23552**
PATENT TRADEMARK OFFICE

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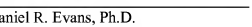

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